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Predictors of Excess Mortality Following Fracture: A Population-Based Cohort Study

L. Joseph Melton III, M.D.[1], **Elizabeth J. Atkinson, M.S.**[2], **Jennifer L. St. Sauver, Ph.D.**[1], **Sara J. Achenbach, M.S.**[2], **Terry M. Therneau, Ph.D.**[2], **Walter A. Rocca, M.D., M.P.H.**[1,3], and **Shreyasee Amin, M.D.C.M., M.P.H.**[1,4]

[1]Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA.

[2]Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA.

[3]Department of Neurology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA.

[4]Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA.

Abstract

To determine the extent to which excess mortality following fractures due to particular causes at specific skeletal sites can be predicted using data about all medical diagnoses, we conducted an historical cohort study among 1991 Olmsted County, Minnesota residents ≥50 years of age who experienced any fracture in 1989-1991 and who were followed passively for up to 22 years for death from any cause. We used a machine learning approach, gradient boosting machine (GBM) modeling, to determine whether the comorbid conditions present at the time of fracture and those that arose subsequently could, in aggregate, identify patients at the greatest increased risk of death. During 21,867 person-years of follow-up, 1245 deaths were observed when 1061 were expected (standardized mortality ratio, 1.2; 95% CI 1.1 to 1.2). Patients presented with a median history of 26 comorbid conditions each as assessed by the Clinical Classification Software system, and 57 each over the total duration of follow-up. Using all available information, the excess deaths could be predicted with good accuracy (c-index ≥0.80) in 89% of the GBM models built for patients with different types of fracture; in one-third of the models, the c-index was ≥0.90. The conditions most prominent in the GBM prediction models were also reflected in the specific causes of death

Address correspondence to Dr. L. Joseph Melton III, Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905. Telephone: (507)284-5550; Telefax: (507)284-1516; melton.j@mayo.edu.

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EJA takes responsibility for the integrity of the data analysis.

that were elevated, suggesting the influence of confounding on the relationship. However, the predominant comorbid conditions were mainly those responsible for mortality in the general population, rather than the specific diseases most closely associated with secondary osteoporosis. To reduce long-term deaths in the fracture population as a whole, a more general approach to the fracture patient is indicated.

Keywords

AGING; FRACTURES; GENERAL POPULATION STUDIES; MORTALITY; OSTEOPOROSIS; STATISTICAL METHODS

Introduction

Although the focus historically has been on survival following hip fractures,[1] it is generally understood that mortality is elevated after the occurrence of most types of fractures.[2,3] Co existing medical conditions (~ comorbidity) are thought to account for much of this excess.[4] For example, Kanis and colleagues estimated that deaths were directly related to hip fracture in 24% of cases and to underlying comorbidity in some general sense in the remaining 76%;[5] likewise, 28% of deaths among patients hospitalized for vertebral fracture were presumably due to the fracture and related complications, leaving 72% unaccounted for.[6] Others have reported similar results,[3,7-14] but there has been no systematic assessment of the specific diseases most responsible. Common chronic diseases account for a substantial proportion of all deaths in the general population,[15] and the Charlson Comorbidity Index,[16] a widely used comorbidity scoring system, focuses on these diseases. However, the Charlson Index ignores most of the disorders known to cause accelerated bone loss (ie, secondary osteoporosis) and to exacerbate fracture risk.[17] It remains uncertain whether this distorts the evaluation of mortality following fracture. Moreover, since fractures at different skeletal sites vary with respect to age, sex, and precipitating cause,[18] one might expect underlying comorbidity patterns to vary as well.[19]

To address this issue, we determined the extent to which a comprehensive assessment of coexisting medical conditions was able to determine which patients were at a risk of death greater than that expected given their age and sex (ie, excess deaths) following fractures of various types, and we identified the diseases most closely associated with these deaths. Rather than selecting a handful of comorbid conditions of interest *a priori*, however, we employed gradient boosting machine (GBM) models, which can combine non-linear relationships and interactions among large numbers of variables with small individual effects.[20] This allowed us to exploit extensive comorbidity data to predict excess mortality following fracture in a large population-based cohort of adults ≥50 years of age, who were followed for up to 22 years.[21] We also investigated results using the well-established Charlson Index. We hypothesized that deaths following pathologic fractures would relate mostly to cancer per se, and that underlying comorbid conditions generally would better predict the excess deaths following fractures that were attributed to moderate trauma than the deaths following fractures due to severe trauma.

Methods

This analysis was based on the long-term follow-up of a large population-based cohort of Olmsted County, Minnesota, residents ≥35 years old who had a fracture during the three-year period, 1989 to 1991.[22] In the original investigation, record review on 9260 potential cases, including institutionalized patients, was completed on all but 74 (0.8%) residents, who had not provided an authorization for review of their medical records for research.[23] Following additional approval by the Institutional Review Boards of Mayo Clinic and the Olmsted Medical Center, we then used data resources of the Rochester Epidemiology Project[24] to passively follow this inception cohort for all-cause mortality.[21] The present investigation extends our previous report by considering the specific causes of death that were observed ("official" underlying cause of death from the State of Minnesota death certificate database, augmented by a search of the National Death Index). Comorbidities, defined as medically-diagnosed diseases,[25] were identified among the subset of subjects who were 50 years old or over, who accounted for 95% of all deaths observed in the original study, using the comprehensive Rochester Epidemiology Project medical records-linkage system. This database includes diagnoses made for outpatients seen in office or clinic consultations, emergency room visits or nursing home care, as well as those recorded for hospital inpatients, at autopsy examination and on death certificates, by essentially all providers of medical care to the residents of Olmsted County.[26] Fractures were classified according to etiology using information about each event that was recorded in the medical record. Acknowledging that bone densitometry predicts the risk of fractures attributed to severe trauma as well as those due to moderate trauma, and that the actual forces involved have rarely been quantified, we separated the fractures into those due to no more than moderate trauma (by convention, equivalent to a fall from standing height or less) and those resulting from severe trauma (eg, motor vehicle accident or a fall from greater than standing height)[27] since we were interested in the potential influence of severe trauma on mortality. Because of their high mortality, we also distinguished the patients whose fractures were caused by a specific pathological process (eg, metastatic malignancy) as determined by their attending physicians. If a patient experienced multiple fractures, only the first one of each type was used in the analysis.

The excess risk of death following fracture was evaluated by comparing the numbers of deaths observed to the numbers expected in this cohort during their follow-up, ie, by computing age- and sex-standardized mortality ratios (SMRs). Patients were followed from fracture until the last clinical visit, but follow-up also included deaths that occurred within one year following their last clinical visit. Underlying cause-specific (http://wonder.cdc.gov) and overall expected mortality rates were based on Minnesota life tables. Ninety-five percent confidence intervals (95% CI) for the SMRs were calculated assuming that the expected rates are fixed and the observed deaths follow a Poisson distribution.

Diagnoses in the early years, which had been classified according to the Hospital Adaptation of the 8th International Classification of Diseases (H-ICD-8),[28] were mapped to corresponding rubrics of the 9th revision of the International Classification of Diseases, Clinical Modification (ICD-9-CM) used after 1997.[29] All diagnoses were then categorized by the Clinical Classifications Software (CCS) system whereby over 14,000 ICD-9-CM

codes are reduced to 283 "clinically meaningful categories,"[30] although only 271 CCS conditions were actually observed in our data. The CCS variables were created by counting the occurrence of at least one ICD-9-CM code within any CCS category that was observed over each subject's entire medical history after age 35 years. Relevant ICD-9-CM diagnoses were also used to calculate the age- and severity-weighted Charlson comorbidity score.[31]

We used the R package, GBM,[32] to build separate prediction models for different types of fractures using the CCS conditions, age as a continuous variable, and sex, and assuming a Poisson error structure. The CCS conditions were modeled as time-dependent covariates. Shrinkage penalization, which controls the rate of optimization in the model, was set at 0.01 (values closer to the maximum value of 1 are computationally faster but less accurate). Tree complexity, which controls the maximum number of interactions in these models, was set at three (ie, 2 and 3-way interactions were allowed) to allow for more complex relationships among the various risk factors. The number of terms in the fit was determined by internal cross-validation to prevent overfitting. Separate GBM models were created to predict excess deaths using the data from all fracture patients, from those with fractures attributed to severe versus no more than moderate trauma and, in the latter group, from patients with fractures at specific skeletal sites. The overall and etiology-specific GBM models were also used to predict excess mortality following the other types of fractures, as was the traditional Charlson Comorbidity Index, which was evaluated at one-year increments.

As an expression of excess mortality discrimination, the concordance statistic (c-index, analogous to the area under a receiver operating characteristic curve) was assessed using the predictive values from the various models.[33] Following the recommendation of other authors,[34] c-index values ≥0.80 were considered good evidence for determining the excess mortality outcome, whereas c-index values close to 0.5 indicated little improvement in prediction beyond chance alone. Subcohorts with less than 20 events were not evaluated because of unstable models. Model calibration was assessed as described elsewhere.[35] Analyses were performed using R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Over the three-year study period, 1989 to 1991, 2619 fractures were experienced by 1991 Olmsted County residents aged 50 years or older, 98% of whom were white by self-report in accordance with the racial composition of the community in this age-group (97% white in 1990). This cohort was subsequently followed for up to 22 years (21,867 person-years), during which time 1245 patients died; these 1245 deaths exceeded the 1061 deaths that were expected (SMR, 1.2; 95% CI 1.1 to 1.2). The age-adjusted SMRs were similar for women and men ($p = 0.149$). After adjusting for sex, the greatest excess risk of death was observed in the youngest age-groups; this excess declined and remained steady at ages beyond 70 years, although it was still higher than expected ($p = 0.009$).

Relative death rates by underlying cause are delineated in Table 1. Excluding 9 Olmsted County residents with an unknown cause of death, 24 residents experienced a fracture attributed by their attending physicians to a local pathological process (mostly metastatic

prostate cancer and lung cancer or multiple myeloma in the men and breast cancer or multiple myeloma in the women). As expected, deaths following a pathologic fracture almost always resulted from malignancy. However, there were so few subjects, and deaths, that pathologic fractures could not be evaluated further. Another 679 subjects experienced a fracture due to severe trauma (motor vehicle accident in 109, fall from greater than standing height in 234, recreational mishap in 58, and occupational or other injury in 278). In this group, the risk of death was significantly increased for accidents (falls, fractures and traumatic amputation or crush injuries) as delineated in Table 1. A final 1282 residents had a fracture that was attributed to minimal or moderate trauma, including 288 fractures where no specific traumatic event was recognized (eg, fractures that occurred in the course of daily activities and those found incidentally); a fall from standing height or less was responsible for the other 994 cases. Those with fractures due to moderate trauma were at increased risk of dying from infections (mostly septicemia), mental (mostly dementia) and nervous system (mostly parkinsonism and Alzheimer's disease) disorders, diseases of the circulatory (mostly chronic heart disease and stroke), respiratory (mostly pneumonia and chronic obstructive pulmonary disease) and genitourinary (mostly renal failure) systems, musculoskeletal diseases (mostly connective tissue disorders and osteoporosis) and accidents (mostly falls).

Only 8 subjects had fracture recorded as the underlying cause of death, including just 2 of the 240 patients who died following a hip fracture. Only 7 patients had osteoporosis listed as the underlying cause. Altogether, 110 of the 1236 patients with a known cause of death had a mention of "fracture" anywhere on the death certificate, whereas "osteoporosis" was mentioned somewhere on 60 death certificates (17 with mention of both fracture and osteoporosis).

SMRs by fracture site and cause are shown in Table 2 for different periods of follow-up. The overall risk of death following fracture was greater than expected for both women and men, especially within the first 5 years of follow-up, and this was also observed for the fractures attributed to no more than moderate trauma. Within that group, excess morality was particularly evident following fractures of the axial skeleton, including the vertebrae, and the proximal femur. There were relatively few excess deaths following the fractures due to severe trauma as a group.

The fracture patients had been attended in the community for an average of 34 years prior to their fracture, and 54,017 CCS conditions (median, 26 per person) had been observed prior to the occurrence of any fracture. Over all follow-up (before and after fracture), 117,169 CCS conditions were observed in the cohort as a whole (median, 57 per person). A greater number of CCS conditions was recorded for women than men (mean, 60 versus 56; $p < 0.001$), and the number per subject increased somewhat with age ($r = 0.2$; $p < 0.001$). As shown in Table 3, the CCS conditions were used to build age-adjusted GBM models to predict the excess risk of death for the same fracture categories that were delineated in Table 2. Although there was considerable variation in the ability of these models to predict subsequent excess deaths on the basis of CCS conditions (c-index, 0.75 to 0.96), and some models were unstable, the overall predictability of death was comparable for women (c-index, 0.89; 95% CI, 0.86-0.91) and men (c-index, 0.89; 95%, CI, 0.86-0.93), as well as for follow-up within 5 years of the fracture (c-index, 0.87; 95% CI, 0.85-0.95) and 5 years or

beyond (c-index, 0.89; 95% CI, 0.87-0.91). Similar results were seen following the moderate trauma fractures that accounted for most of the total. When the modeling was restricted to use only of the conditions that were recorded sometime prior to the fracture (Appendix Table A), however, the GBM models were much less capable of discriminating the excess deaths. The overall c-index was only 0.74 (95% CI, 0.72-0.76) compared with 0.88 (95% CI, 0.86-0.90) when all CCS conditions were used.

Because c-index values are artificially high when models and predictions are based on the same dataset, as was the case here, we also applied the specific GBM models developed for one type of fracture to predict excess deaths following the other types of fracture; we also compared these results with a similar GBM model built using the diagnoses included in the Charlson Comorbidity Index, as well as with the Charlson Index itself (Table 4). Results across the three main GBM models were generally quite consistent for predicting overall excess deaths (c-index, 0.86 to 0.88) or deaths following fractures due to severe trauma (c-index, 0.89 to 0.91) or following fractures resulting from no more than moderate trauma (c-index, 0.82 to 0.86). Likewise, the different models were fairly comparable for predicting excess deaths in follow-up within or beyond 5 years of the original fracture, although calibration data suggested that the predictions were a little low for the first 5-year period (observed/predicted, 1.16-1.58) and a little high for follow-up beyond 5 years (observed/predicted, 0.60-0.96). Moreover, there was little reduction in performance when a model developed on one type of fracture was applied to another. Figures were lower for the Charlson Index, whether it was used as designed or the relevant diagnoses were incorporated into a GBM model (Table 4).

Notably, conditions that comprise the Charlson Comorbidity Index frequently appeared in the different GBM models (Table 5), and they were often causes of the deaths that were observed in the fracture cohort as a whole (Table 1). Moreover, the comorbid conditions associated with an excess risk of death were similar for patients with a fracture due to severe trauma compared to those with a fracture attributed to no more than moderate trauma, although the relative importance of specific disease categories varied between the two groups (Table 5). The top variables were also similar for the various fracture subtypes (data not shown).

Discussion

It is generally understood that underlying comorbid conditions, defined here as medically-diagnosed diseases,[25] are partially responsible for the excess deaths following hip and vertebral fractures[4] and even distal forearm fractures in a subset of elderly patients.[36] However, previous studies of this issue have typically evaluated a limited number of diagnoses, often obtained by self-report or from administrative data. In the present investigation, we used GBM modeling to interrogate all diagnoses documented in comprehensive (inpatient and outpatient) community medical records for a large population-based cohort of patients with fracture.[26] Rather than deal with thousands of individual rubrics, diagnoses were grouped into a much smaller number of CCS conditions,[30] which have been shown to predict death following hip fracture.[34] The fracture patients had a median 57 different CCS conditions each, and this information was able to predict excess

mortality with good accuracy (c-index >0.80) in 89% of the GBM models that we computed. Indeed, the c-index was 0.90 or more in a third of the models. Unfortunately, the prediction of excess deaths was not nearly so effective when only the comorbid conditions recorded prior to fracture were used, as the c-index values for those GBM models rarely exceeded 0.80.

GBM models are particularly well suited for dealing with massive amounts of information without the need for prior annotation of variables, and we previously showed that areas under receiver operating characteristic curves approached 1.0 for discriminating patients with vertebral fractures or distal forearm fractures from controls in GBM models that incorporated hundreds of imaging variables.[20] It is important to point out that the inclusion of comorbid conditions recorded in the distant past, or those having no association with the risk of excess death, does not “dilute” the power of GBM models such as these. Thus, the models were virtually unchanged when baseline comorbidity data were limited to the 10-year or 5-year periods prior to fracture. A corresponding limitation of the GBM approach, however, is that the resulting predictive models are specific to the dataset. They are difficult to generalize to other settings since there is no formula to share, and they may be hard to interpret from a pathophysiologic perspective. Neither issue was relevant to this study, which was designed to evaluate the possibility of predicting subsequent excess deaths using the comorbidity data that are increasingly available to attending physicians from electronic health records. More important, perhaps, is the observation that the clinical conditions most prominent in the various GBM mortality prediction models were frequently those represented in the Charlson Comorbidity Index. This suggests that the excess deaths among fracture patients, especially those deaths that occur long after the fracture, can mainly be explained on the basis of the conditions predominantly responsible for mortality in the general population.

We had expected cancer-related deaths to be elevated among the patients with pathologic fractures. This is an issue of confounding, ie, the underlying malignancy may cause both the fracture and the subsequent death, although the occurrence of a pathologic fracture signifies an increased risk of death.[37] Given the predominant role of acute trauma, we also expected that a GBM model based on underlying comorbidity would not perform well in predicting excess deaths following the fractures due to severe trauma, but it worked as well as the other models. Moreover, although excess deaths were relatively less common following the severe trauma than the moderate trauma fractures, the distribution of causes of death was similar in the two groups. Noteworthy in the moderate trauma group were deaths from dementia, parkinsonism, chronic obstructive lung disease, renal failure, systemic connective tissue disorders and falls. Since these are risk factors for fracture as well,[19] confounding may also play a role in the relation between some underlying conditions (or their treatments) and death following the fractures that were attributed to no more than moderate trauma. The Charlson Comorbidity Index includes some of these conditions, yet it performed less well than the GBM models because they were not only built but also tested on this specific dataset.

This investigation had a number of strengths, including the use of a large population-based cohort comprised of all community residents age 50 years or over who experienced any

fracture (not just traditional osteoporotic fractures) from any cause (not just moderate trauma) in the 3-year period, 1989 to 1991.[22] These unselected subjects were followed passively from the time of the first fracture of each type during the study period (though not necessarily the first-ever lifetime fracture of that type) for up to 22 years for vital status through the medical records-linkage system of the Rochester Epidemiology Project.[38] This system provides access to the records of essentially all providers of medical care to local residents,[24] and it allowed us to retrieve all diagnoses made by these providers for each subject over their entire period of residency in the community.[26] These diagnoses were categorized using the CCS system that provides "more or less homogeneous clinical categories,"[30] which then supported a systematic assessment of comorbid conditions.

The study also had limitations. In particular, we evaluated disease diagnoses *per se* rather than specific deficits (eg, frailty) more proximate to death, and the role of such deficits requires further investigation. These diagnoses were made by many different providers in multiple settings and may not have equivalent specificity. Moreover, errors may have occurred in mapping H-ICD-8 diagnostic rubrics to ICD-9-CM codes and in the assignment of the official underlying cause of death. These potential problems were minimized by the use of broad comorbidity and mortality groupings. Also, because of the demographic composition of the community, the vast majority of fractures occurred among white subjects, and any estimates for other ethnic groups would be unstable. Although death rates following fracture appear to be greater in nonwhites,[39] the majority of age-related fractures in this country occur in the white population, and hip fracture incidence rates from Olmsted County are comparable to estimates of hip fracture incidence for United States whites generally.[40]

Conclusions

Most previous studies of fracture-related mortality have focused on one type of fracture at a time, prompting a notion that predictors of reduced survival may be unique to each fracture type. This is bolstered by the fact that the etiology of different fractures does vary in many important respects (eg, the relative contributions of fall-related trauma versus bone loss). By contrast, our data suggest that the conditions most responsible for the long-term excess risk of death are similar for fractures of different types and, indeed, are mostly those responsible for mortality in the general population[15] rather than the endocrine/metabolic conditions uniquely associated with secondary osteoporosis.[17] This finding has important clinical implications insofar as a narrow approach to management that focuses on preventing fractures in patients with secondary osteoporosis is unlikely to be effective in reducing long-term deaths in the fracture population as a whole. Given the wide range of comorbid conditions implicated by these data, a more general approach to these patients is indicated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Observed (O) Versus Expected (E) Underlying Causes of Death Among Olmsted County, Minnesota, Residents ≥ 50 Years of Age Following a Fracture (Fx) in 1989-91

	All fractures (N=1982)		Severe trauma Fx (N=679)		Moderate trauma Fx (N=1282)		Pathological Fx (N=24)	
Underlying Cause of Death	**O/E**	**SMR (95% CI)†**	**O/E**	**SMR (95% CI) †**	**O/E**	**SMR (95% CI) †**	**O/E**	**SMR (95% CI)†**
Infectious and parasitic diseases	15/10	1.5 (0.8-2.5)	3/3.5	0.9 (0.2-2.5)	13/6.7	**2.0 (1.04-3.3)**	0/0.0	--
Neoplasms	214/206	1.0 (0.9-1.2)	67/81	0.8 (0.6-1.1)	129/126	1.0 (0.9-1.2)	22/0.6	**39 (24-58)**
Endocrine, nutritional and metabolic disease and immunity disorders	38/38	1.0 (0.7-1.4)	9/13	0.7 (0.3-1.3)	25/25	1.0 (0.6-1.5)	0/0.1	--
Disease of the blood and blood-forming organs	4/5.0	0.8 (0.2-2.0)	1/1.5	0.7 (0.02-3.7)	2/3.6	0.6 (0.1-2.0)	0/0	--
Mental disorders	101/48	**2.1 (1.7-2.5)**	20/14	1.5 (0.9-2.3)	78/35	**2.2 (1.7-2.7)**	0/0.2	--
Diseases of the nervous system and sense organs	69/49	**1.4 (1.1-1.8)**	18/17	1.1 (0.6-1.7)	51/33	**1.5 (1.1-2.0)**	0/0.2	--
Diseases of the circulatory system	466/419	**1.1 (1.01-1.2)**	120/129	0.9 (0.8-1.1)	346/294	**1.2 (1.1-1.3)**	2/1.4	1.4 (0.2-5.0)
Diseases of the respiratory system	141/104	**1.4 (1.1-1.6)**	34/35	1.0 (0.7-1.4)	109/71	**1.5 (1.3-1.8)**	0/0.3	--
Diseases of the digestive system	40/32	1.2 (0.9-1.7)	10/11	0.9 (0.5-1.7)	31/22	1.4 (0.96-2.0)	0/0.1	--
Diseases of the genitourinary system	32/23	1.4 (0.9-2.0)	5/7.4	0.7 (0.2-1.6)	29/16	**1.8 (1.2-2.6)**	0/0.1	--
Diseases of the skin and subcutaneous tissue	4/1.4	2.9 (0.8-7.4)	1/0.4	2.4 (0.1-13)	2/1.0	2.0 (0.2-7.4)	0/0	--
Diseases of the musculoskeletal system and connective tissue	22/9.0	**2.4 (1.5-3.7)**	2/2.9	0.7 (0.1-2.6)	21/6.2	**3.4 (2.1-5.2)**	0/0	--
Congenital anomalies	1/1.0	1.0 (0.03-5.6)	0/0.4	--	1/0.6	1.6 (0.04-8.8)	0/0	--
Symptoms, signs, and ill-defined conditions	12/32	**0.4 (0.2-0.7)**	3/9.2	**0.3 (0.1-0.95)**	9/23	**0.4 (0.2-0.8)**	0/0.1	--
Injury and poisoning	77/30	**2.6 (2.0-3.2)**	22/10	**2.1 (1.3-3.2)**	56/20	**2.8 (2.1-3.7)**	0/0.1	--

†Standardized mortality ratios (SMR) and 95% confidence intervals. Expected deaths by underlying cause are for the Minnesota population of comparable age and sex (http://wonder.cdc.gov/). Statistically significant ($p < 0.05$) associations are bolded.

Nine subjects with unknown underlying cause of death were excluded from this analysis. If a person had more than one fracture during the time period, (s)he could be included in more than one trauma category.No deaths were observed from "complications of pregnancy, childbirth, and the puerperium."

Table 2

Observed (O) Versus Expected (E) Deaths Among 1991 Olmsted County, Minnesota, Residents ≥ 50 Years of Age Following a Fracture in 1989-91, by Skeletal Site, Sex and Time-Interval After Fracture

	All follow-up						0 to < 5 years after fracture						≥ 5 years after fracture					
	Women			Men			Women			Men			Women			Men		
Fracture cause/site	**Subjects**	**O/E**	**SMR (95% CI)†**	**Subjects**	**O/E**	**SMR (95% CI)†**	**Subjects**	**O/E**	**SMR (95% CI)†**	**Subjects**	**O/E**	**SMR (95% CI)†**	**Subjects**	**O/E**	**SMR (95%CI)†**	**Subjects**	**O/E**	**SMR (95% CI)†**
Any fracture	1395	889/777	**1.1 (1.1-1.2)**	596	356/284	**1.2 (1.1-1.4)**	1395	349/275	**1.3 (1.1-1.4)**	596	166/95	**1.8 (1.5-2.0)**	971	540/502	1.1 (0.99-1.2)	399	190/190	1.0 (0.9-1.2)
Severe trauma fracture	386	182/197	0.9 (0.8-1.1)	299	139/143	1.0 (0.8-1.2)	386	55/50	1.1 (0.8-1.4)	299	51/36	**1.4 (1.1-1.9)**	319	127/146	0.9 (0.7-1.03)	230	88/107	0.8 (0.7-1.01)
Moderate trauma fracture	997	697/586	**1.2 (1.1-1.3)**	289	209/150	**1.4 (1.2-1.6)**	997	282/225	**1.2 (1.1-1.4)**	289	108/60	**1.8 (1.5-2.2)**	653	415/361	**1.2 (1.04-1.3)**	170	101/90	1.1 (0.9-1.4)
Vertebral fracture	283	228/176	**1.3 (1.1-1.5)**	69	57/41	**1.4 (1.04-1.8)**	283	116/75	**1.5 (1.3-1.8)**	69	35/18	**1.9 (1.3-2.7)**	150	112/101	1.1 (0.9-1.3)	33	22/23	1.0 (0.6-1.4)
Other axial fracture	195	161/111	**1.4 (1.2-1.7)**	97	71/50	**1.4 (1.1-1.8)**	195	79/50	**1.6 (1.2-2.0)**	97	37/19	**1.9 (1.4-2.6)**	102	82/61	**1.4 (1.1-1.7)**	54	34/31	1.1 (0.8-1.5)
Distal forearm fracture	198	122/119	1.0 (0.8-1.2)	18	8/9.7	0.8 (0.4-1.6)	198	27/34	0.8 (0.5-1.1)	18	3/2.6	1.2 (0.2-3.4)	157	95/85	1.1 (0.9-1.4)	15	5/7.2	0.7 (0.2-1.6)
Other upper limb fracture‡	117	77/69	1.1 (0.9-1.4)	29	26/12	**2.1 (1.4-3.2)**	117	28/24	1.2 (0.8-1.7)	29	8/4.6	1.8 (0.8-3.5)	80	49/45	1.1 (0.8-1.4)	20	18/7.5	**2.4 (1.4-3.8)**
Proximal femur fracture	183	159/109	**1.5 (1.2-1.7)**	42	37/13	**2.8 (2.0-3.9)**	183	85/62	**1.4 (1.1-1.7)**	42	26/9.0	**2.9 (1.9-4.2)**	87	74/47	**1.6 (1.2-2.0)**	14	11/4.0	**2.7 (1.4-4.9)**
Other lower limb fracture‡	137	81/67	1.2 (0.95-1.5)	45	25/23	1.1 (0.7-1.6)	137	31/22	1.4 (0.9-2.0)	45	15/8.9	1.7 (0.9-2.8)	98	50/45	1.1 (0.8-1.5)	29	10/14	0.7 (0.4-1.4)

†Standardized mortality ratios (SMR) and 95% confidence intervals. Statistically significant associations are bolded.

‡Excluding fractures of the hands and feet, which were not associated with excess deaths.

Table 3

Predictability (C-Index and 95% Confidence Interval) of Excess Deaths (Observed Deaths Adjusted for Expected) Among Olmsted County, Minnesota, Residents ≥ 50 Years of Age Following a Fracture in 1989-91, Adjusted for Age and All Medical Conditions As Assessed by the Clinical Classification Software (CCS) System, by Fracture Type, Sex and Time-Interval After Fracture

	All follow-up			0 to < 5 years after fracture			≥ 5 years after fracture		
Fracture site/cause	**Women**	**Men**	**Both sexes**	**Women**	**Men**	**Both sexes**	**Women**	**Men**	**Both sexes**
Any fracture	0.89 (0.86-0.91)	0.89 (0.86-0.93)	0.88 (0.86-0.90)	0.88 (0.85-0.92)	0.90 (0.85-0.94)	0.87 (0.85-0.90)	0.90 (0.81-0.92)	0.91 (0.87-0.96)	0.89 (0.87-0.91)
Severe trauma fracture	0.92 (0.87-0.96)	0.91 (0.87-0.96)	0.91 (0.88-0.94)	0.89 (0.82-0.96)	0.96 (0.88-1.00)	0.93 (0.88-0.99)	0.93 (0.88-0.99)	0.92 (0.86-0.98)	0.91 (0.87-0.95)
Moderate trauma fracture	0.87 (0.84-0.89)	0.89 (0.85-0.93)	0.86 (0.84-0.88)	0.88 (0.84-0.91)	0.90 (0.85-0.96)	0.86 (0.83-0.89)	0.87 (0.84-0.90)	0.93 (0.87-0.99)	0.88 (0.85-0.90)
Vertebral fracture	0.84 (0.80-0.88)	0.91 (0.82-0.99)	0.85 (0.82-0.89)	0.87 (0.81-0.92)	0.77 (0.66-0.87)	0.86 (0.81-0.91)	0.87 (0.81-0.93)	0.90 (0.77-1.00)	0.88 (0.82-0.93)
Other axial fracture	0.86 (0.81-0.91)	0.87 (0.79-0.94)	0.87 (0.83-0.92)	0.90 (0.83-0.97)	0.78 (0.83-0.97)	0.89 (0.83-0.94)	0.93 (0.86-1.00)	0.77 (0.66-0.81)	0.91 (0.85-0.97)
Distal forearm fracture	0.92 (0.86-0.97)	-	0.90 (0.85-0.96)	0.80 (0.68-0.91)	-	0.83 (0.72-0.94)	0.88 (0.82-0.94)	-	0.89 (0.83-0.95)
Other upper limb fracture[†]	0.93 (0.86-1.00)	0.85 (0.73-0.97)	0.91 (0.85-0.97)	0.82 (0.71-0.94)	-	0.85 (0.74-0.95)	0.84 (0.76-0.93)	-	0.84 (0.77-0.91)
Proximal femur fracture	0.82 (0.77-0.87)	0.85 (0.75-0.95)	0.82 (0.77-0.86)	0.81 (0.74-0.88)	0.90 (0.78-1.00)	0.75 (0.69-0.81)	0.79 (0.72-0.86)	-	0.87 (0.80-0.93)
Other lower limb fracture[†]	0.77 (0.71-0.83)	0.92 (0.80-1.00)	0.87 (0.81-0.93)	0.94 (0.83-1.00)	-	0.81 (0.72-0.90)	0.75 (0.68-0.83)	-	0.87 (0.79-0.94)

[†]Excluding fractures of the hands and feet, which were not associated with excess deaths.

Dashes indicate an unstable estimateof the standardized mortality ratiodue to a small number of events.

Table 4

Ability of a Gradient Boosting Machine (GBM) Mortality Model Based on All Follow-upand Using Clinical Classification System (CCS) Conditions as Developed for One Type of Fractureto Predict Excess Deaths Following Another Fracture Type Compared to Predictions from the Charles Comorbidity Index Itself or From a GBM Model Using the Charlson Index Diagnoses. C-Index Is Shown

Fracture (Fx) cause	All Fx model [CCS conditions]	Severe trauma Fx model [CCS conditions]	Moderate trauma Fxmodel [CCS conditions]	All Fx model [Charlson diagnoses]	All Fx model [Charlson score]
All follow-up					
All Fx mortality	**0.88 (0.86-0.90)**	0.86 (0.84-0.87)	0.88 (0.86-0.89)	**0.80 (0.78-0.81)**	**0.80 (0.78-0.82)**
Severe trauma Fx mortality	0.90 (0.87-0.94)	**0.91 (0.88-0.94)**	0.89 (0.85-0.92)	0.81 (0.78-0.85)	0.80 (0.77-0.83)
Moderate trauma Fx mortality	0.86 (0.84-0.88)	0.83 (0.81-0.85)	**0.86 (0.84-0.88)**	0.78 (0.76-0.80)	0.78 (0.76-0.80)
< 5 years after Fx					
All Fx mortality	0.88 (0.85-0.90)	0.85 (0.83-0.88)	0.87 (0.84-0.89)	0.81 (0.78-0.83)	0.78 (0.75-0.80)
Severe trauma Fx mortality	0.91 (0.85-0.97)	0.91 (0.86-0.97)	0.90 (0.84-0.96)	0.81 (0.75-0.87)	0.79 (0.73-0.84)
Moderate trauma Fx mortality	0.85 (0.82-0.88)	0.82 (0.79-0.85)	0.85 (0.82-0.88)	0.78 (0.75-0.81)	0.77 (0.73-0.80)
≥ 5 years after fracture					
All Fx mortality	0.89 (0.87-0.91)	0.87 (0.85-0.89)	0.88 (0.86-0.91)	0.80 (0.78-0.82)	0.81 (0.79-0.84)
Severe trauma Fx mortality	0.91 (0.87-0.95)	0.91 (0.87-0.95)	0.89 (0.85-0.93)	0.82 (0.78-0.86)	0.82 (0.78-0.86)
Moderate trauma Fx mortality	0.87 (0.84-0.90)	0.84 (0.81-0.86)	0.87 (0.85-0.90)	0.78 (0.76-0.81)	0.80 (0.77-0.83)

Bolding indicates c-index for a specific model applied to its own excess mortality outcomes.

Table 5

Top 20 Conditions in Selected Fracture (Fx) Gradient Boosting MachineMortality Models Predicting Excess Deaths Based on All Follow-upand Using Clinical Classification (CCS) conditions. Relative Influence Is Shown in Parentheses

Mortality model based on all follow-up			
All Fx model [CCS conditions]	**Severe trauma Fx model [CCS conditions]**	**Moderate trauma Fx model [CCS conditions]**	**All Fx model [Charlson diagnoses]**
Age (13.4)	Age (10.9)	Age (12.0)	Age (34.4)
Male sex (0.1)	Male sex (0.0)	Male sex (0.2)	Male sex (0.4)
Respiratory failure; insufficiency; arrest (8.3)	Aspiration pneumonitis; food/vomitus (12.9)	Respiratory failure; insufficiency; arrest (8.9)	Dementia (17.5)
Aspiration pneumonitis; food/vomitus (7.5)	Respiratory failure; insufficiency; arrest (7.0)	Malignant neoplasm without specification of site (6.2)	Metastatic Solid Tumor (14.5)
Malignant neoplasm w/o specification of site (5.3)	Malignant neoplasm without specification of site (3.9)	Aspiration pneumonitis; food/vomitus (5.5)	Congestive Heart Failure (13.2)
Acute & unspecified renal failure (4.2)	Other gastrointestinal disorders (3.6)	Cancer of pancreas (4.2)	Moderate/Severe Renal Disease (6.6)
Other screening for suspected conditions (NOT mental disorders or infectious disease) (3.8)	CHF; Nonhypertensive (3.5)	Acute & unspecified renal failure (3.8)	Cerebrovascular Disease (4.3)
Cardiac arrest & ventricular fibrillation (2.7)	Acute & unspecified renal failure (3.4)	Substance-related disorders (3.8)	Myocardial Infarction (4.0)
Schizophrenia and other psychotic disorders (2.6)	Attention-deficit, conduct, & disruptive behavior disorders (3.3)	Delirium, dementia, other cognitive (3.3)	Hemiplegia (1.3)
CHF; Nonhypertensive (2.5)	Bacterial infection; unspecified site (2.3)	Other screening for suspected conditions (NOT mental disorders or infectious disease) (3.0)	Diabetes (1.0)
Cancer of pancreas (2.5)	Cancer of bronchus; lung (2.1)	CHF; Nonhypertensive (2.8)	Peripheral Vascular Disease (0.5)
Delirium, dementia, other cognitive (2.1)	Other bone disease & musculoskeletal deformities (2.0)	Cardiac arrest & ventricular fibrillation (2.6)	Moderate/Severe Liver Disease (0.5)
Secondary malignancies (2.1)	Shock (1.9)	Schizophrenia and other psychotic disorders (2.3)	Ulcer (0.5)
Immunizations & screening for infectious disease (1.8)	Other screening for suspected conditions (NOT mental disorders or infectious disease (1.7)	Pneumonia (1.8)	Rheumatologic Disease (0.4)
Pneumonia (1.6)	Secondary malignancies (1.3)	Nutritional deficiencies (1.6)	Diabetes with Organ Damage (0.3)
Fracture of neck of femur (1.5)	Immunizations & screening for infectious disease (1.3)	Cancer of bronchus; lung (1.6)	Other Cancer (0.3)
Cancer of bronchus; lung (1.5)	Cancer of liver and intrahepatic bile duct (1.2)	Septicemia (1.4)	Mild Liver Disease (0.2)
Chronic ulcer of skin (1.4)	Schizophrenia and other psychotic disorders (1.2)	Disorders of lipid metabolism (1.4)	Chronic Pulmonary Disease (0.1)
Disorders of lipid metabolism (1.3)	Sprains and strains (1.2)	Acute cerebrovascular disease (1.2)	Aids (0.0)
Acute cerebrovascular disease (1.2)	Other skin disorders (1.1)	Chronic ulcer of skin (1.2)	

Mortality model based on all follow-up			
All Fx model [CCS conditions]	**Severe trauma Fx model [CCS conditions]**	**Moderate trauma Fx model [CCS conditions]**	**All Fx model [Charlson diagnoses]**
Paralysis (1.1)	Other diseases of veins & lymphatics (1.1)	Pleurisy; pneumothorax; pulmonary collapse (1.0)	
Nutritional deficiencies (1.1)	Septicemia (1.0)	Fluid & electrolyte disorders (0.9)	

†Relative influence relates to the contribution of each variable to the model, and the weights add to 100.[41] Since the GBM models contain up to 271 CCS conditions and the Charlson Comorbidity Index only 17 diagnoses, the values appear greater in the latter analysis.